REMARKS/ARGUMENTS

Claims 119-123 are pending in this application and are rejected on various grounds. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 119-123 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention lacks a credible, specific and substantial asserted utility or a well established utility."

Claims 119-123 remain further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention."

The Examiner continues to maintain the rejections based on the gene amplification assay (pages 2-5 of the instant Office action). But, as indicated in their response filed January 19, 2006, instead of the gene amplification assay, the instantly pending claims were amended to rely upon assay 94 or 'the glucose/FFA uptake assay,' (Example 158) for patentable utility of PRO1182 polypeptides. Accordingly, any of the Examiner's rejections /references or discussions referring to the gene amplification assay are not currently addressed. Those rejections referring to the glucose/FFA uptake utility are discussed below.

Arguments

Previously, Applicants had erroneously referred to PRO1182 as a molecule that inhibits glucose/FFA uptake by adipocytes. Instead, as discussed below, PRO1182 enhances glucose/ FFA uptake by adipocytes. Support for this amendment is clearly present in Example 158, which discloses the glucose/ FFA uptake assay as follows:

> Primary rat adipocyte cells are plated on a 96 well plate and incubated overnight with media supplemented with PRO1182 polypeptide. After the initial overnight incubation, samples of the media are taken at hour 4 and hour 16 and residual glycerol, glucose and FFA are measured. After the hour 16 sample is taken, insulin is added to the media and the adipocytes are allowed to incubate for an additional 4 hours. After this final 4 hour incubation, another sample is taken and residual glycerol, glucose and FFA is measured again.

As a control, identical incubations and samplings were performed on cells that were incubated overnight in media, initially supplemented with insulin rather than the PRO1182 polypeptide. Results were scored as positive in the assay if the uptake is greater than 1.5 times (stimulatory), or as inhibitory, if the uptake was less than 0.5 times the uptake of the insulin control. As PRO1182 resulted in more than 1.5 times the uptake of the insulin control, PRO1182 tested positive as a **stimulator** of (or enhanced) glucose/FFA uptake in adipocyte cells (specifically, see Example 158). Therefore, one skilled in the art would know that antibodies to PRO1182, especially agonistic antibodies, would be useful in enhancing glucose uptake ny adipovyte cells.

Applicants had submitted supportive references, Tafuri *et al.*, Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000), to show that, the utility for agents modulating glucose/FFA uptake was well known in the art at the time of filing of the instant application, for instance, in the treatment of conditions such as obesity, diabetes, and hyper- or hypo-insulinemia. Therefore, one skilled in the art would have known how to use of PRO1182 in the treatment of conditions such as obesity, diabetes, and hyper- or hypo-insulinemia, based on the glucose/FFA uptake assay results for PRO1182.

In the recent Office action, the Examiner herself acknowledges the teachings of the articles by the Applicants, indicating that "each of the references cited by Applicants teaches that the agents utilized in the assays *enhance* glucose uptake.....**Disorders such as obesity, diabetes, and hyper- or hypo-insulinemia are characterized by a reduction in the amount of glucose entering all cells, including adipocytes.....Therefore, as emphasized by Tafuri et al., Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000), one skilled in the art is searching for agents that will enhance glucose uptake into adipocyte cells**." (page 7, line 2 through page 8, line 2).

Therefore, based on the instant results demonstrating the ability of the PRO1182 polypeptides to enhance glucose uptake in the glucose/ FFA assay, one skilled in the art, as the Examiner acknowledges, would readily recognize that PRO1182 polypeptides are usefulin the treatment of disorders benefiting from this biological activity, such as obesity, diabetes, or hyper- or hypo-insulinemia.

The Examiner however maintained the previous rejection on page 8 of the Office action and says "Tafuri *et al.*, Sandouk *et al.*, Goldwaser *et al.*, Mueller *et al.* (1998) and Mueller *et al.* (2000) teach different methodologies for the measurement of glucose uptake in adipocyte cells as compared to the glucose assay of the instant specification....None of the references utilizes the same grading scale disclosed in the instant specification, but instead report dose-response curves. The instant specification does not report any specific cell numbers or statistical differences and there is no indication in the specification as to how PRO1182 inhibited glucose uptake as compared to control or whether the results were significant." The Examiner concludes that the PRO1182 peptide is not in currently available form, and the asserted utility is not substantial. Applicants once again strongly disagree with the utility standards utilized by the Examiner in this rejection.

Applicants respectfully submit that, compliance with the utility requirement does not require that the methodology used in making the invention be the same as those used in the referenced or related art. What is important is that the assay be a well- recognized assay and that guidelines be provided in the specification to perform the assay, including assay read-out, if applicable. As discussed in their response dated January 19, 2006, Applicants submitted that the glucose uptake assay is a well-accepted assay in the art for identifying molecules that modulate glucose uptake. The fact remains that the results of the adipocyte glucose/FFA uptake assay were positive, indicating that PRO1182 polypeptides and PRO1182 agonistic antibodies are useful in *enhancing* glucose uptake by adipocyte cells. The instant specification also clearly discusses the controls used in the assay. For example, the results of the glucose uptake assay were scored as positive if the uptake was greater than 1.5 times (stimulatory), or as inhibitory, if the uptake was less than 0.5 times the uptake of the insulin control. Since PRO1182 resulted in more than 1.5 times the uptake of the insulin control, PRO1182 tested positive as a **stimulator** (or enhancer) of glucose/FFA uptake in adipocyte cells.

The Examiner's requirement for specific "cell numbers and statistical results" are also clearly not a requirement of the utility standards set by the USPTO. Applicants submit that the glucose uptake assay described herein is a comparative assay, meaning that the utility is based upon a comparison of relative uptake levels between a well-accepted and known control like insulin (for glucose uptake) and a test molecule like PRO1182. Useful pharmacological

information is obtained when a relative difference is observed in this assay. In addition, the need for "cell numbers or statistical results" is a misplaced requirement, and is a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval of a pharmacological or diagnostic assay, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new assay, will indeed ask for actual numerical data, statistical analysis, and other specific information before any assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States.

Accordingly, Applicants respectfully submit that the Examiner's comments fail to support a *prima facie* case of lack of utility and in fact, based on the results of the glucose uptake assay. Instead, PRO1182 polypeptides and PRO1182 agonistic antibodies are in currently available form, and their asserted utility is specific, credible and substantial. Therefore, the Examiner is requested to reconsider and withdraw the present rejection under 35 U.S.C. §101 and §112, first paragraph.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C34**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 10, 2006

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